REMARKS

The Abstract is amended herein.

Claim 7 is amended herein by deleting "preventing or".

No new matter is presented.

I. Response to Objection to the Specification

In paragraph 3 of the Action, the Examiner objects to the Abstract of the disclosure as containing legal phraseology of "said". The Examiner requests appropriate correction to comply with 37 C.F.R. § 1.72(b) of the MPEP.

The Abstract is amended herein, thereby obviating the objection to the specification.

Accordingly, Applicants respectfully request withdrawal of the objection.

II. Response to Claim Rejections Under 35 U.S.C. § 112

In paragraph 4 of the Action, claims 2-7 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for treating hot flash, allegedly does not reasonably provide enablement for preventing hot flash.

Claim 7 is amended to delete the recitation of "preventing or", thereby obviating the rejection.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, 1st paragraph.

III. Response to Claim Rejections Under 35 U.S.C. § 103

In paragraph 5 of the Action, claims 2-7 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Furuya et al (US 6,297,379) as evidenced by Hara et al (The Journal of Clinical Endocrinology & Metabolism, 2003, Vol. 88, No. 4, pp. 1697-1704) and Freedman (American Journal of Human Biology, 2001, Vol. 13, pp. 453-464).

In paragraph 6 of the Action, claims 2-5 and 7 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Furuya et al (US 6,048,863) as evidenced by Hara et al as applied to claim 2, and as further evidenced by Freedman.

In paragraph 7 of the Action, claims 2-4 and 7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Furuya et al. (US 6,001,850) as evidenced by Hara et al and Freedman as applied to claims 2 and 7.

In paragraph 8 of the Action, claims 2-4 and 7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Furuya et al. (US 6,187,788) as evidenced by Hara et al and Freedman as applied to claims 2 and 7.

Applicants respectfully traverse the rejections.

In each rejection, the Examiner's finding of obviousness is partially based on the assertion that each of the four Furuya et al patents teaches treatment or prevention of sex hormone-dependent diseases and hot flash is a sex hormone dependent condition.

Furuya et al actually teaches that the disclosed compounds are useful for preventing and/or treating sex hormone dependent cancers, prostatic hypertrophy, hysteromyoma, endometriosis, precocious puberty, amenorrhea, premenstrual syndrome, multiocular ovary syndrome and acne. See, for example, column 11, lines 52-58 of the '379 patent, column 45,

lines 49-57 of the '863 patent and the Abstracts of the '850 and '788 patents. Furuya et al also teaches that the disclosed compounds are useful for the regulation of reproduction in males and females.

Furuya et al does not specifically teach or suggest the treatment or prevention of hot flashes. The diseases or conditions disclosed in Furuya et al are caused, exaggerated or maintained by sex hormones. Contrary to this, hot flashes occur under conditions where sex hormone levels are lowered as discussed below. Thus, Furuya et al does not teach or suggest the treatment of hot flashes.

Hara et al does not remedy the deficiencies of Furuya et al. Hara et al relates to hormone-dependent diseases such as endometriosis, uterine leiomyomas and breast cancer (page 1701, 2nd column) and does not specifically relate to hot flashes.

Freedman et al also fails to remedy the deficiencies of Furuya et al.

The Examiner states that it would have been considered obvious that hot flashes are a sex hormone-dependent condition (page 8, lines 9-10 of the Office Action). The Examiner's position is such that, since the thienopyridine derivative of the present invention is known to have GnRH antagonizing activity and such a thienopyridine derivative can be used for treatment of sex hormone-dependent diseases, it would have been obvious to a person skilled in the art to use the thienopyridine derivative of the present invention for the treatment of hot flashes.

However, Applicants submit that the Examiner is incorrect because hot flashes cannot be said to be a sex hormone-dependent condition, though it has certain relations with sex hormones.

The relationship between hot flashes and sex hormones is not so simple. The paragraph bridging pages 458-459, Endocrinology A Estrogens, of the Freedman reference discloses as

follows: "However, estrogens alone do not appear responsible for hot flashes since there is no correlation between the presence of this symptom and plasma, urinary or vaginal levels."

Hot flashes are considered to have a relation with a sex hormone (estrogen) because hot flashes occur at menopause or when treatment is carried out by lowering sex hormone levels.

However, it has been revealed that hot flashes occur under conditions where sex hormone levels are **lowered** as mentioned below. According to this revealed knowledge, it would have been expected that there would be a possibility that the thienopyridine derivative of the present invention rather causes hot flashes because such a derivative is known to have GnRH antagonizing activity, i.e., sex hormone level lowering-activity.

Thus, the present invention employing compounds of formula (I) as recited in the present claims to treat hot flashes would not have been obvious to a person skilled in the art.

As mentioned above, it has been revealed that hot flashes occur under conditions where sex hormone levels are lowered. The attached copy of "The American Journal of Medicine (2005), Vol. 118 (12B), 124S-130S discloses the report relating to hot flashes by Dr. Freedman, who is the same author of the Freedman reference cited by the Examiner. At page 124S, Abstract, there is the following description:

> Although hot flashes accompany the withdrawal of estrogen at menopause, the decline in estrogen levels is not sufficient to explain their occurrence. Elevated sympathetic activation acting through co-adrenergic receptors contributes to the initiation of hot flashes.

In view of the above, Applicants submit that one of ordinary skill in the art would not have had a reasonable expectation of success of achieving the presently claimed method of treating hot flashes based on the teachings of Furuya et al, Freedman and/or Hara et al.

Accordingly, Applicants respectfully request withdrawal of the §103 rejections.

IV. Response to Obviousness-Type Double Patenting Rejections

In paragraph 9 of the Action, claims 4 and 7 are rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claim 13 of Furuya et al. (US 6,001,850) as evidenced by Freedman.

In paragraph 10 of the Action, claims 4 and 7 are rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claim 8 of Furuya et al. (US 6,048,863) as evidenced by Freedman.

In paragraph 12 of the Action, claims 4 and 7 are rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claim 4 of Furuya et al. (US 6,187,788) as evidenced by Freedman.

In response to these rejections, Applicants submit that the arguments above with respect to the Furuya et al references and Freedman traversing the obviousness rejections apply to these obviousness-type double patenting rejections as well, and thus withdrawal of these rejections is respectfully requested.

V. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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Hot flashes: behavioral treatments, mechanisms, and relation to sleep

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KEYWORDS:
Exercise;
Hot flashes;
Menopause;
Paced respiration;
Sleep

Hot flashes are the most common symptom of the climacteric and occur in about 75% of perimenopausal and postmenopausal women in Western societies. Although hot flashes accompany the withdrawal of estrogen at menopause, the decline in estrogen levels is not sufficient to explain their occurrence. Elevated sympathetic activation acting through central α_2-adrenergic receptors contributes to the initiation of hot flashes, possibly by narrowing the thermoneutral zone in symptomatic women. Hot flashes are then triggered by small elevations in core body temperature acting within this narrowed zone. A relaxation-based method, paced respiration, has been shown in 3 controlled investigations to significantly reduce objectively measured hot flash occurrence by about 50% with no adverse effects. In 6 studies of physical exercise, however, investigators did not find positive effects on hot flashes, possibly because exercise raises core body temperature, thereby triggering hot flashes. Although many epidemiologic studies have found increased reports of sleep disturbance during the menopausal transition, recent laboratory investigations have not found this effect, nor have they found that hot flashes produce disturbed sleep. Therefore, sleep complaints in women at midlife should not routinely be attributed to hot flashes or to menopause.

Hot flashes are the most common symptom of the climacteric and occur in about 75% of perimenopausal and postmenopausal women in the United States.[1] The frequency of hot flashes can range from 5 per year to 50 per day, with great variations among individuals or even within an individual. They generally persist for 1 to 5 years, but in some women they can continue for as long as 44 years.[2] There is no accepted metric for measuring severity of hot flashes.

Hot flashes are an exaggerated heat dissipation response and comprise widespread cutaneous vasodilation and profuse upper body sweating.[3] They are described as sensations of heat, sweating, flushing, chills, clamminess, and anxiety.[2]

There are few major risk factors for menopausal hot flashes. Two recent investigations[4,5] found that high body mass index (BMI) is directly related to hot flash frequency. This may be caused by the effect of increased insulation from body fat, resulting in elevated core body temperature (T_c), which triggers hot flashes.[6] Cigarette smoking has also been found to increase the risk of hot flashes,[4,5] possibly through the effect on estrogen metabolism or through the thermogenic effects of nicotine.[7]

The opinions offered at the National Institutes of Health (NIH) State-of-the Science Conference on Management of Menopause-Related Symptoms and published herein are not necessarily those of the National Institute on Aging (NIA) and the Office of Medical Applications of Research (OMAR) or any of the cosponsoring institutes, offices, or centers of the NIH. Although the NIA and OMAR organized this meeting, this article is not intended as a statement of Federal guidelines or policy.

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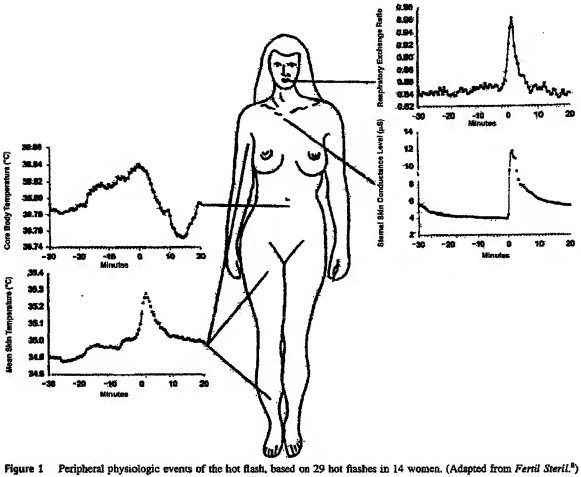

Figure 1 Peripheral physiologic events of the hot flash, based on 29 hot flashes in 14 women. (Adapted from *Ferril Steril.*[8])

Physiologic events of the hot flash

Peripheral vasodilation, demonstrated by increased skin temperature and blood flow, occurs during hot flashes in all body areas that have been investigated (Figure 1). Skin temperature increases in the digits, cheek, forehead, upper arm, chest, abdomen, back, calf, and thigh.[8–12] Blood flow in the finger, hand, calf, and forearm also increases during hot flashes.[10–12] These changes typically occur within the first few seconds of the reported onset of the flash.[10]

Sweating and skin conductance, an electrical measure of sweating, also increase during hot flashes. Molnar[9] measured the whole body sweat rate to be about 1.3 g/min in 1 subject. We simultaneously recorded measures of sweating and skin conductance from the sternum during 29 hot flashes in 14 women.[13] There was a close temporal correspondence between both measures that increased significantly. Measurable sweating occurred during 90% of the flashes.

Increased sternal skin conductance has proved to be the best objective marker of menopausal hot flashes to date. A 2-μS increase in conductance measured within 30 seconds corresponded with 95%,[13] 90%,[14] and 80%[15] of patient reports of hot flashes in 4 separate studies. No such responses were recorded in premenopausal or asymptomatic postmenopausal women.[13,14] Measurements of finger temperature and blood flow were less predictive of hot flash occurrence.[15]

The skin conductance measurement is particularly useful for the evaluation of treatment studies because it can be recorded outside the laboratory over prolonged intervals and does not require the patient's intervention. Using the same recording methods with ambulatory monitors, investigators found an 86% agreement between the skin conductance criterion (2 μS/30 sec) and patient event marks.[15] A second study found an agreement rate of 77%.[14] A more recent study using a smaller, solid-state recorder found a concordance rate of 72% in 18 patients with breast cancer who had hot flashes.[16]

Endocrinology of hot flashes

Although hot flashes accompany the withdrawal of estrogen at menopause, the decline in estrogen levels is not sufficient to

explain their occurrence. There is no correlation between hot flash occurrence and plasma,[17] urinary,[18] or vaginal[18] levels of estrogen, nor are there differences in plasma levels between symptomatic and asymptomatic women.[19–22] Additionally, clonidine reduces hot flash frequency without changing circulating estrogen levels.[23]

The search for a hot flash trigger began with the observation of a temporal correspondence between luteinizing hormone (LH) pulses and hot flashes.[24] However, later research showed that women with isolated gonadotropin deficiency had hot flashes but no LH pulses and women with hypothalamic amenorrhea had LH pulses but no hot flashes.[25] Moreover, hot flashes occur in women with LH suppression from gonadotropin-releasing hormone analogues,[26] in women with pituitary insufficiency and hypoestrogenism,[27] and in women who underwent hypophysectomy who have no LH pulses.[28]

An opioidergic mechanism was then considered as a basis for hot flashes. Lightman and colleagues[29] found that naloxone infusion reduced the number of hot flashes and LH pulses in a small group of symptomatic women, but DeFazio and associates[30] were unable to replicate these effects. Studies of β-endorphin levels during hot flashes have produced conflicting results.[31] Thus, there is no consistent evidence of the involvement of an opiate system in hot flashes.

Norepinephrine (NE) plays a major role in thermoregulation acting, in part, through α_2-adrenergic receptors. Plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), the main metabolite of NE, were found to be significantly higher in symptomatic than in asymptomatic postmenopausal women[32] and increased significantly more during hot flashes.[32,33] Clinical studies had shown that clonidine, an α_2-adrenergic agonist that reduces brain NE, significantly reduced hot flash frequency.[34,35] Further study then showed that injection of yohimbine, an α_2-adrenergic antagonist that raises levels of brain NE, provoked hot flashes in symptomatic women and that injection of clonidine ameliorated them.[36] Taken together, these data suggest that elevated sympathetic activation, acting through central α_2-receptors, plays a role in the initiation of hot flashes. Because estrogens modulate these receptors,[37] it is possible that menopausal estrogen withdrawal is involved in this mechanism.

Thermoregulation and hot flashes

In homeotherms, T_c is regulated between an upper threshold for sweating and a lower threshold for shivering. Between these thresholds is a neutral zone within which major thermoregulatory responses (sweating, shivering) do not occur.[38] Fine thermoregulatory adjustments within the neutral zone are effected by variations in peripheral blood flow. According to this theory, the heat dissipation responses of the hot flash (sweating, peripheral vasodilation) would be triggered if T_c were elevated such that the upper threshold was crossed. We showed that there is a circadian rhythm of hot flashes that is related to the circadian rhythm of T_c: hot flashes are more frequent when T_c is highest.[39] In the course of the latter study, the majority of hot flashes were found to be preceded by small but statistically significant elevations in T_c as measured by an ingested telemetry pill. This finding was replicated in 2 further studies.[40,41] Thus, we believe that these T_c elevations constitute an element of the hot flash–triggering mechanism.

Previous studies showed that peripheral heating and warm ambient temperatures can provoke hot flashes,[42] suggesting that the upper threshold is lowered in symptomatic women. We therefore measured the sweating and shivering thresholds and calculated the width of the thermoneutral zone in symptomatic and asymptomatic postmenopausal women.[43] We assessed the sweating threshold by raising T_c using peripheral heating and bicycle exercise, and found that the thermoneutral zone was 0.0°C in the symptomatic women and 0.4°C in the asymptomatic women, mainly owing to a lowering of the sweating threshold in the former group. The T_c sweating thresholds were the same for heating and for exercise, and they were accompanied by objective and subjective hot flashes in every case. Sweat rates in the symptomatic women were twice those of the asymptomatic women ($P < 0.05$). No hot flashes occurred in the asymptomatic women. Thus, we believe that hot flashes are triggered by T_c elevations acting within a greatly reduced thermoneutral zone in symptomatic postmenopausal women (**Figure 2**). A hot flash, consisting of sweating and peripheral vasodilation, is triggered when T_c reaches the upper threshold. T_c then declines and, when the lower threshold is crossed, shivering occurs. In a subsequent study, we found that the T_c elevations also occur in asymptomatic women.[44] Therefore, the critical factor in the etiology of hot flashes is the narrowing of the thermoneutral zone.

Animal studies have shown that an increase in brain levels of NE narrows the width of the thermoneutral zone.[45] Conversely, clonidine reduces NE release, raises the sweating threshold, and lowers the shivering threshold. Thus, we suggest that elevated brain level of NE is likely to narrow the thermoregulatory interthreshold zone in symptomatic postmenopausal women (Figure 2).

Behavioral treatment for hot flashes

Because elevated sympathetic activation has been implicated in the genesis of hot flashes, relaxation-based procedures have been used to treat them. In the first investigation,[46] postmenopausal women with frequent hot flashes were randomly assigned to receive 6 weekly sessions of progressive muscle relaxation and slow, deep breathing (paced respiration) or α-wave electroencephalographic (EEG) biofeedback (placebo control procedure). The relaxation procedure significantly reduced both objective symptoms recorded in the laboratory and diary-recorded hot flash frequency by about 50% compared with the control procedure. A second study was performed in which a group of

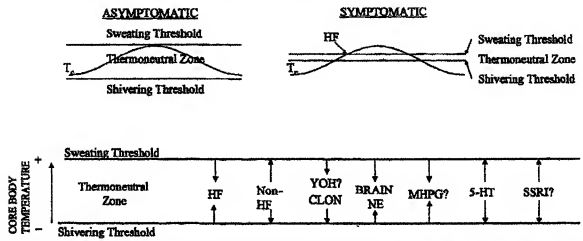

Figure 2 Small core body temperature (T_c) elevations acting within a reduced thermoneutral zone trigger hot flashes (HFs) in symptomatic postmenopausal women. The thermoneutral zone is narrowed in symptomatic women (with HF) compared with asymptomatic women (non-HF). Elevated brain norepinephrine (NE) in animals reduces this zone. Yohimbine (YOH) elevates brain NE and should reduce the zone. Conversely, clonidine should widen it. 5-HT = serotonin; MHPG = 3-methoxy-4-hydroxyphenylglycol (the primary NE metabolite); SSRI = serotonin-selective reuptake inhibitor.

subjects received slow deep breathing alone, a second group received muscle relaxation exercises alone, and a third group received α-wave EEG biofeedback.[47] Treatment outcome was assessed by ambulatory monitoring of sternal skin conductance responses, which were used to define hot flashes. Only the paced respiration group showed a significant decline (50%) in hot flash frequency. There were no significant changes shown in the 2 other groups. To determine whether reduced sympathetic activation was the mechanism by which paced respiration ameliorates hot flashes,[48] we therefore measured plasma MHPG, epinephrine, NE, cortisol, and platelet α_2-receptors during paced respiration and α-wave EEG biofeedback in 24 symptomatic women. Treatment outcome was again assessed by ambulatory monitoring of sternal skin conductance. The paced respiration group showed a significant decline in hot flash frequency (again about 50%) compared with no change in the control group. However, there was no significant change in any biochemical measure for either group. Thus, the mechanism through which paced respiration reduces hot flash frequency remains to be determined. The last controlled study[49] randomly assigned symptomatic postmenopausal women to receive relaxation response training (paced respiration plus mental focusing), a reading control group, or no treatment. The relaxation response group showed a significant decline in hot flash intensity but not frequency. There was no significant change in the other groups. Thus, we conclude that paced respiration training produces a significant decline in hot flash frequency and, perhaps, intensity. There is no known harmful effect.

Physical exercise also has been used as a potential treatment for hot flashes. There have been 3 randomized clinical trials and 3 other studies. The largest randomized clinical trial (N = 173)[50] compared a moderate-intensity exercise intervention with a stretching control group over 1 year. Exercise significantly increased the severity of hot flashes with no change in their occurrence. A Japanese study[51] compared 20 women in a 12-week education and exercise program with 15 no-treatment controls. There were no significant effects on hot flashes. A Swedish study[52] compared 15 women in a 3 times weekly exercise program with 15 women receiving oral estradiol. There was no change in hot flash frequency in the exercise group, but a 90% decrease in hot flashes was observed in the estradiol group.

A large (N = 1,323), population-based, retrospective study in Linkoping, Sweden,[53] found no significant effect of moderate exercise (1 to 2 hr/wk) on hot flash occurrence. A case-control study (N = 171)[54] at a health maintenance organization in California also found no effect of exercise on hot flashes. A retrospective, population-based study in Lund, Sweden (N = 6,917),[55] found that vigorous exercise (>3 hr/wk) was associated with significant reductions in hot flash frequency and intensity in a small number of women (4%), but this was confounded by other factors.

Taken together, the above studies do not demonstrate significant, positive effects of physical exercise on menopausal hot flashes. Our finding that exercise triggers hot flashes in the laboratory may, in part, explain these results.[43]

Hot flashes and sleep

Many epidemiologic studies have found increased reports of sleep disturbance during the menopausal transition (**Table 1**).[56–69] It is generally believed that hot flashes produce arousals and awakenings from sleep, leading to fatigue and, possibly, impaired performance. However, this

Table 1 Do hot flashes and sleep disturbance occur with menopause?

Study	Type	Hot Flashes	Sleep Disturbance
McKinlay and Jefferys (1974)[56]	Cross-sectional	+	−
Ballinger (1976)[57]	Cross-sectional	ND	+
Bungay et al (1980)[58]	Cross-sectional	+	+
Hunter et al (1986)[59]	Cross-sectional	+	+
Anderson et al (1987)[60]	Clinic	+	+
Matthews et al (1990)[61]	Longitudinal	+	−
Hunter (1992)[62]	Cross-sectional	+	+
Holte (1992)[63]	Longitudinal	+	−
Shaver and Paulsen (1993)[64]	Cross-sectional	+	−
Avis et al (1994)[65]	Longitudinal	+	+
Baker et al (1997)[66]	Clinic, cross-sectional	+	+
Kuh et al (1997)[67]	Longitudinal	+	+
Owens and Matthews (1998)[68]	Cross-sectional	ND	−
	Longitudinal	ND	+
Kravitz et al* (2003)[69]	Longitudinal	+	+

ND = not done.
*Study of Women's Health Across the Nation (SWAN).

notion is challenged by 2 recent laboratory investigations.[21,70] In a study by Freedman and Roehrs,[21] symptomatic and asymptomatic postmenopausal women and premenopausal women of similar ages were recorded under controlled laboratory conditions. They were screened to eliminate those (1) with any drug use; (2) with any sleep, physical, or mental disorder; or (3) with a BMI >30. There were no group differences on any sleep stage measure, on sleep or fatigue questionnaires, or on any performance test. When hot flashes occurred (mean ± SD, 5.2 ± 2.9 per night), they tended to follow, rather than precede, arousals and awakenings. These data provide no evidence that hot flashes produce sleep disturbance in symptomatic postmenopausal women.

We replicated these findings in a more recent investigation. A total of 18 symptomatic and 6 asymptomatic postmenopausal women and 12 women with eumenorrhea of similar ages were recorded on warm (30°C ambient), neutral (23°C), and cold (18°C) nights. There was no significant effect of room temperature for any group on any physiologic sleep measure. All subjects expected worse sleep on the warm versus the cold night ($P < 0.01$), but only the symptomatic women reported lighter and less refreshing sleep on the warm versus the cold night ($P < 0.005$). These results demonstrate that reports of worse sleep in symptomatic women at warm ambient temperatures are due to expectancies rather than to physiologic effects.

These findings are strongly supported by those of a large recent epidemiologic investigation.[70] The Wisconsin Sleep Cohort Study measured sleep quality by complete laboratory polysomnography and by self-reports in a probability sample of 589 premenopausal, perimenopausal, and postmenopausal women. Sleep quality was not worse in perimenopausal or postmenopausal women or in symptomatic compared with asymptomatic women on any measure. Taken together, these studies suggest that sleep complaints in women at midlife should not routinely be attributed to hot flashes or to menopause. Rather, the underlying disorder (e.g., sleep apnea) should be ascertained, and appropriate treatment should be based on these findings.

Summary

Hot flashes are triggered by small elevations in T_c acting within a reduced thermoneutral zone in symptomatic postmenopausal women. This reduction is probably caused by estrogen withdrawal and elevated central sympathetic activation, among other factors. Relaxation-based procedures incorporating paced respiration are safe and effective in ameliorating hot flashes. Physical exercise, however, is not efficacious in the treatment of hot flashes. Although most epidemiologic studies report increased sleep disturbance at menopause, this is not supported by laboratory physiologic studies, nor has the role of hot flashes in producing sleep disturbances been proved.

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